Original Research Paper

Volume-8 | Issue-4 | April-2018 | PRINT ISSN No 2249-555X

General Medicine

COMPARATIVE ANALYSIS OF ANTICOAGULANT EFFICACY BETWEEN HEPARIN AND BIVALIRUDIN DURING PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

Dr. Kavya Annapareddy Post graduate student, Department of General Medicine, Deccan College of Medical Sciences, Hyderabad, Telangana.

Dr. M. Kaleemullah Khan Professor, Department of General Medicine, Deccan College of Medical Sciences, Hyderabad, Telangana

Dr.Syed Mohammed Ali* Professor and HOD, Department of General Medicine, Deccan College of Medical Sciences, Hyderabad, Telangana *Corresponding Author

ABSTRACT The aim of the present study is to investigate efficacy of the anti-coagulants bivalirudin versus heparin across the spectrum of acute coronary syndrome (ACS). It is a prospective, open labelled, observational comparative study carried out at Princess Esra Hospital and Owaisi Hospital and Research Centre, Hyderabad.Anti-coagulant efficacy of heparin and bivalirudin was compared in ACS cases undergoing percutaneous coronary intervention (PCI) by assessing major adverse cardiovascular events (MACE). The number of cases receiving heparin was 120 and those receiving bivalirudin was 103.Assessment of net adverse clinical events (NACE) and stent thrombosis was done at 30 days and one year after the procedure. The proportion of cases for baseline characteristics such as gender, smokers, cases with hypertension, with angina, STEMI, and NSTEMI were comparable in both heparin and bivalirudin groups. However, the number of diabetics was 77 out of 103 (74%) in bivaluridin group and 60% (72 out of 120) in the heparin group. It is concluded that all the patients with ST-elevation myocardial infarction (MI) should be treated with anti-coagulant therapy as soon as possible after the diagnosis. The choice of anti-coagulant agent should depend upon the treatment strategy and condition of each patient. Bivaluridin has been found to be associated with less incidences of bleeding (Major bleeding one case (0.8%) in heparin group while none in the bivalirudin group). However, higher rates of stent thrombosis were recorded in bivalirudin group (5 cases 4.9%) compared to only 2 cases (1.7%) in the group on heparin ($p<0.05$)). Further studies are required to prove superiority of bivalirudin over heparin interms of clinical outcomes.

KEYWORDS :

Introduction

Coagulation is the naturally occurring process that prevents blood loss. It is the most important step for decreasing bleeding through different cascade steps. Rupture of an atherosclerotic plaque is considered as the initiating event in acute coronary syndrome (ACS) and persistent thrombotic occlusion at the site of plaque rupture results in acute myocardial infarction.

Morbidity in acute coronary syndrome reduced drastically with the peri operative use of drugs like Aspirin, Clopidogrel, so much so that most of the mortality was attributed too increase in bleeding tendency due to potent newer antiplatelet agents. However in cases of acute myocardial infarction with persistent ST segment elevation, intravenous anticoagulation is recommended in all patients undergoing PCI (primary percutaneous intervention).

In order to further reduce mortality rate newer aspects in the management were tried. Newer anticoagulants were tried since heparin has an indirect effect on thrombin and has no effect on the clot bound thrombin (1). Bivalirudin a new anticoagulant which has less side effects and has direct action on thrombin including clot bound thrombin was introduced (2, 3). Initial trials with this drug revealed that it was equally efficacious and with decrease incidence of bleeding as a result significantly reduced mortality and decrease incidence of bleeding. Results of clinical trials to date suggest bivalirudin as a viable alternative to the use of heparin combined with (GPI) glycoprotein IIb/IIIa inhibitor (4). In the HORIZONS AMI-trial study it was observed that bivalirudin was strongly associated with reduced cardiac mortality even in patients without any bleeding after accounting for all adverse events known to be reduced by bivalirudin (bleeding, thrombocytopenia, re-infarction) (5).

The aim of the present study was to investigate efficacy of bivalirudin versus heparin across the spectrum of ACS cases and the comparison of anticoagulant efficacy of heparin and bivalirudin was compared in cases undergoing PCI by assessing major adverse cardiac events (MACE). The number of cases receiving heparin was 120 and those bivalirudin was 103. Assessment of net adverse clinical events (NACE) and stent thrombosis was done at 30 days and one year after the procedure. Bivalirudin was expected to be non inferior to heparin and may have less NACE during PCI in ACS cases.

Patients and Methods

This was a prospective, open labeled, observational comparative study carried out at Princess Esra Hospital and Owaisi Hospital and Research Centre, Hyderabad over a period of two years (June 2015-July 2017). Prior to the initiation of study an Institutional ethics committee approval was taken and an informal consent was obtained from each patient.

A total of 120 patients receiving heparin during PCI in ACS and 103 patients receiving bivalirudin during PCI in ACS were included in the study as per the pre defined inclusion criteria. As per the inclusion criteria patients of acute coronary syndrome (LIA/NSTEMI /STEMI/IBBB) above the age of 18 years were included. Exclusion criteria was as follows : 1. Pre-medication with Low molecular weight heparin (LMWH)/fondaparinux, 2. Heparin induced thro mbocytopenia (HIT) 3. Current use of warfarin 4. Intracerebral stroke 5. Stroke or TIA within the past 6 months 6. Platelets less than 1,00,000/mm^3 7. Hemoglobin less than 10 gm % 8. Coagulotpathy 9. Bleeding diathesis 10. Genito-urinary gastro intestional bleeding within previous 2 months etc.

Procedure

All the patients studied received aspirin and ticagrelor as a concomitant medication. 103 patients were given bivalirudin. The recommended dose of bivalirudin is an intravenous (IV) bolus dose od 0.75 mg/kg followed by an infusion of 1.75 mg/kg /hr for the duration of the PCI procedure. Five minutes after the bolus dose has been administered, an activated clotting time (ACT) was performed and an additional bolus of 0.3 mg/kg was given if needed. GP IIb/IIIa inhibitor (GPI) administrations were considered if event was present. Continuation of the infusion following PCI for upto 4 hours post procedure was optimal. After 4 hours, an additional IV infusion of bivalirudin was initiated at a rate of 0.2 mg/kg/hr (low rate infusion) for upto 20 hours, if needed.

The recommended dose of heparin is an IV bolus of 70 U/kg followed by subsequent boluses if activated clotting time (ACT) was less than 200 sec. GP IIb/IIIa inhibitor (GPI) administration was considered in case of any event.

The patients were followed up at 30 days and 1 year after the procedure

and assessed for net adverse clinical events (NACE) and for stent thrombosis. The NACE was considered as conglomerate of death, myocardial infarction, target lesion revascularization, stroke and major secondary end point.

Observations and results

Details of the baselines characteristics of the patients on heparin and bivalirudin are given in table 1. These characteristics were mean age number of male cases, smoking, hypertension, diabetes, renal disease, hypercholesterolemia, angina, STEMI (ST segment elevation myocardial infarction) NSTEMI, (non ST segment elevation MI) target vessel LMCA (left main coronary artery, LAD (left anterior descending artery, LCX (left circumflex artery) and RCA (right coronary artery). Details of net adverse clinical events (NACE) are also given. Statistically significant differences were noted for the proportion of cases with diabetes (72/120, 60% in the group on heparin and 77/103, 74.8% in the group on bivalirudin) (p=0.02). Significant difference (p value 0.022) was also noted in LMCA vessel involvement. 9.7% cases in bivalirudin group and 2.5% in the group receiving heparin as a target vessel. LAD was involved as a target vessel with a frequency of 63.3% in the ACS cases receiving heparin and 36.9% cases receiving heparin in those on bivalirudin (p value 0.000). As for the right coronary artery involvement was concerned significantly increased frequency (71.8%) was noted in bivalirudin group compared to the group of patients on heparin (59.2%) (p 0.048) (table1)

PCI procedure was carried out through radial or femoral arteries. In heparin group 80 (66.7%) procedures were done via radial artery and 41 (34.2%) via femoral artery. In bivalirudin group 54 (52.4%) procedures were done through radial artery and 49 (47.8%) via femoral artery (Table 1)

In the present study follow up of all the cases patients of both heparin and bivalirudin groups were taken up after 30 days and 12 months of the procedure. Details of the prevalence of various clinical end points are depicted in table2. The various clinical end points given were cardiac death, MI, TLR (Target lesion revascularization), TVR (Target vessel revascularization), stroke, major bleeding , minor bleeding, stent thrombosis and NACE. The results of the follow up studies showed lack of any statistically significant difference between the two groups of patients both at 30 days and 12 months after the PCI procedure. (Table 2)

PCI was performed via radial approach in 80 patients on heparin and 54 patients on bivalirudin. The prevalence of various clinical end points in the patients who underwent PCI via radial route are outlined in table 3. No statistically significant difference could be noted for any of the clinical end points in the two groups.

Discussion

The primary PCI is now considered as a standard treatment for patients with acute coronary syndrome (ACS) significantly reducing major adverse cardiovascular events. It is known that coronary artery rupture initiates ACS by activating the coagulation cascade and the adjunctive antiplatelet as well as antithrombotic therapy is necessary to minimize peri-procedural and post procedural thrombotic events. However the use of these agents is frequently associated with an increase in the incidence of bleeding, which is itself associated with a higher mortality (6). The use of heparin as an anticoagulant in patients undergoing PCI is not without adverse effects. Heparin induced thrombocytopenia (HIT) has been the most common and serious side effect of heparin (7). Moreover heparin has been associated with increased incidences of major bleeding after the PCI. Hence to overcome these complications use of direct thrombin inhibitors was applied in patients undergoing PCI (3). Studies were carried out to compare the anticoagulant efficacy of heparin with that of bivalirudin in ACS cases during PCI as bivalirudin acts a direct thrombin inhibitor (4). Bivalirudin provides potent and effective control of thrombin activity and has been proved as a useful and effective therapeutic agent in a broad spectrum of patients with acute coronary syndrome undergoing PCI. Despite of its theoretical advantages in clinical practice bivalirudin superiority over heparin is doubted (8). Hence the present study was carried-out with the objective of comparing anti-coagulation efficacy of bivalirudin with heparin during percutaneous transluminal coronary angioplasty.

In the present study, the mean age of patients in bivalirudin and heparin groups was 59.38±11.11 years and 57.96±9.86 years respectively. In the HORIZON-AMI trial (5), the ages of the patients in both the groups were similar to those of patients in the present study. The numbers of male patients in the present study were 85 and 93 in bivalirudin and heparin groups, respectively. The proportion of males is similar to other previous studies (9-12).

Hypertension was extensively present in both the groups of patients in the present study (81.6% in bivalirudin group and 73.6% in the heparin group) indicating that the percentage of cases with hypertension in the present study was higher than that reported in the HORIZON-AMI (5) trial where 55.2% cases were hypertensive in bivalirudin group and 51.8% in the heparin group.

The proportion of diabetics was significantly higher in the bivalirudin group (74.8%) compared to that in heparin group (60.0%) (p <0.02) in the present study. In various other studies the number of diabetic patients had been significantly lesser than the present study (5, 10-12). Diabetes has been related to greater incidences of MACE in numerous patients undergoing PCI, this has been probably a substantial factor towards greater rates of stent thrombosis and death in patients of bivalirudin group in the present study.

The most common target vessel in the heparin group of present study was LAD (63.3%) and in bivalirudin group it was RCA (71.8%). These results are similar to those reported in the HORIZONS-AM trial. With regards to NACE rate no significant differences were found in the two groups of patients.

Bleeding is among the most common in-hospital complications of PCI and is independently and strongly associated with long-term adverse outcomes, including MI, stroke and death. A frequent source of bleeding is the arterial access site, a radical approach rather than traditional femoral approach for primary PCI is a safe, and effective technique to reduce access site related bleeding, vascular complications and death (13, 14). In the present study majority of the patients in heparin group were approached through radial route, while in bivalirudin group, both the routes were accessed equally.Radial in 52.4%; formoral in 47.6% (Table 1). Bleeding was observed in the bivalirudin group in patients accessed via radial route. Out of 3 cases of bleeding in patients on heparin after 12 month follow-up one was a major bleeding case and 2 were of minor bleeding (Table 3). Thus it can be postulated that bivalirudin decreases the chances of bleeding compared to heparin in patients accessed via radial approach. Since the first trials, consistent reduction in major bleeding risk with bivalirudin has been reported (10, 15, 16). As for the incidence of stent thrombosis (ST) was concerned higher incidnce was recorded in bivalirudin group compared to heparin group, but the difference was not statistically significant (Table-2).

Conclusion

All the patients with ST-elevation myocardial infarction should be treated with anti-coagulant therapy, which should be given as soon as possible after the diagnosis. The choice of anticoagulant agent depends upon the treatment strategy and condition of each patient.

- Bivalirudin has been found to be associated with less incidences of bleeding but on the contrary higher rates of stent thrombosis.
- Heparin causes more incidences of major bleeding; therefore the peri-proceedural monitoring of dose of heparin should be adjusted and standardized dose of heparin should be used instead of higher doses.
- All the clinical outcomes of the study proved to be statistically insignificant to prove superiority of bivalirudin over heparin, hence further studies are required to prove the same.

Acknowledgement

The authors aknowledge the help extended by Dr. Mohd Ishaq (Prof & HOD), and Dr. N parveen(assistant professor) Salar E MillatResearch Centre PEH, in the preparation of this manuscript.

Tables:

Table 1: Baseline characteristics of patients on heparin and bivalirudin

Variables	Heparin N=120	Bivalirudin	P value
Age distribution (Mean ± SD)	57.96 ± 9.86	59.38 ± 11.11	0.376
Male, n (%)	93 (77.5%)	85 (82.5%)	0.351

Smoking, n (%)	19 (15.8%)	12 (11.7%)	0.368
Hypertension, n (%)	88 (73.3%)	84 (81.6%)	0.145
Diabetes, n (%)	72 (60%)	77 (74.8%)	0.02
Renal disease, n (%)	11 (9.2%)	3 (2.9%)	0.055
Hypercholesterolemia, n (%)	1 (0.8%)	1 (1.0%)	0.914
Angina, n (%)	57 (47.5%)	51 (49.5%)	0.764
STEMI, n (%)	44 (36.7%)	44 (42.7%)	0.357
NSTEMI n (%)	13 (10.8%)	8 (7.8%)	0.434
Target vessel			
LMCA, n (%)	3 (2.5%)	10 (9.7%)	0.022
LAD, n (%)	76 (63.3%)	38 (36.9%)	0.000
LCX, n (%)	31 (25.8%)	32 (311%)	0.387
RCA, n (%)	71 (59.2 %)	74 (71.8%)	0.048
Route			
Radial, n (%)	80 (66.7%)	54 (52.4%)	0.037
Femoral, n (%)	41 (34.2%)	54 (52.4%)	0.003

STEMI: ST segment elevation myocardial infarction, NSTEMI: non-ST segment elevated myocardial infarction, LMCA: left main coronary artery, LAD: left anterior descending, LCX: left circumflex artery and RCA: right coronary rtery and NACE: net adverse cardiac events

Table 2: Clinical endpoints in the study population after 30 days and 12 months follow up

Endpoints	Heparin N=120	Bivalirudin	P value
30 days			
Death, n (%)	2 (1.7%)	4 (3.9%)	0.418
MI, n (%)	1 (0.8%)	0 (0%)	1.000
TLR, n (%)	1 (0.8%)	0 (0%)	1.000
TVR, n (%)	0 (0%)	0 (0%)	-
Stroke, n (%)	0 (0%)	1 (1.0%)	0.462
Major bleeding, n (%)	0 (0%)	0 (0%)	-
Minor Bleeding, n (%)	2 (1.7%)	2 (1.9%)	0.212
Stent thrombosis, n (%)	1 (0.8%)	2 (1.9%)	0.597
NACE, n (%)	4 (3.3%)	5 (4.9%)	0.584
12 months			
Death, n (%)	5 (4.2%)	8 (7.8%)	0.253
MI, n (%)	2 (1.7%)	0.(0%)	0.501
TLR, n (%)	1 (0.8%)	0 (0%)	1.000
TVR, n (%)	0 (0%)	2 (1.9%)	0.212
Stroke, n (%)	0(0%)	1 (1.0%)	0.462
Major bleeding, n (%)	1 (0.8%)	0 (0%)	1.000
Minor Bleeding, n (%)	2 (1.7%)	2 (1.9%)	0.212
Stent thrombosis, n (%)	2 (1.7%)	5 (4.9%)	0.253
NACE, n (%)	9 (7.5%)	9 (8.7%)	0.808

MI: myocardial infarction, TLR: Target lesion revascularization, TVR: Target vessel revascularization, an NACE: net adverse cardiac events.

Table 3: Clinical endpoints in the radial approaches for PCI after 30 days and 12 months follow-up

Endpoints	Heparin N=120	Bivalirudin	P value
30 days			
Death, n (%)	2 (2.5%)	2 (3.7%)	1.000
MI, n (%)	1 (1.3%)	0 (0%)	1.000
TLR, n (%)	1 (1.3%)	0 (0%)	1.000
TVR, n (%)	0 (0%)	0 (0%)	-
Stroke, n (%)	0 (0%)	0 (0%)	-
Major bleeding, n (%)	0 (0%)	0 (0%)	-
Minor Bleeding, n (%)	2 (2.5 %)	0 (0%)	0.515
Stent thrombosis, n (%)	1 (1.3%)	1 (1.9%)	1.000
NACE, n (%)	4 (5 0%)	2 (3.7%)	1.000
12 months			
Death, n (%)	3 (3.8%)	4 (7.4%)	0.439
MI, n (%)	2 (2.5%)	0.(0%)	0.505
TLR, n (%)	1 (1.3%)	0 (0%)	1.000
TVR, n (%)	0 (0%)	2 (3.7%%)	0.161
Stroke, n (%)	0(0%)	0 (0%)	-
Major bleeding, n (%)	1 (1.3%)	0 (0%)	1.000
Minor Bleeding, n (%)	2 (2.5%)	0 (0%)	0.515
Stent thrombosis, n (%)	1 (1.3%)	2 (3.7%)	0.565
NACE, n (%)	7 (8.7%)	4 (7.4%)	1.000

MI: myocardial infarction, TLR: Target lesion revascularization, TVR: Target vessel revascularization, an NACE: net adverse cardiac events.

REFERENCES

1. Weitz J1, Leslie B, Hudoba M. Thrombin binds to soluble fibrin degradation poducts where it is protected from inhibition by heparin-antithrombin-independent inhibitory Circulation. 1998; 97 (6): 544-52.
2. Lefkovits J., Topol EJ. Direct thrombin inhibitors in cardiovascular medicine. Circulation. 1994; 90 (3): 1522-36.
3. Bittle J, Strong J., Brinker J, Ahmed W, Meckel C Chaitman B et al. Treatment with Bivalirudin (hirulog) as compared with heparin during PTCA, for unstable or post infarction angina: Hirulog Angioplasty study investigators. N. Engl. J.Mede.
4. Lehman SJ, chew DP. Bivaluridin in percutaneous coronary intervention. Vascular health and risk management. 2006; 2 (4): 357.
5. Stone G.W, Clayton T., Deliargyris EN, Prats J, Mehran R, Pocock SJ, Reduction in cardiac mortality with bivaluridin in patients with and without major bleeding: The Horizons-AMI trial (Harmonizing outcomes with Revascularization and stents in acute myocardial Infarctions). Journal of the American college of cardiology. 2014; 63 (1): 15-20.
6. Fahmi G, Wolfrum M, De Maria GL, Banning AP, Benedetto U, Kharbanda RK. Prolonged High-Dose bivalirudin infusion reduces major bleeding without increasing stent thrombosis in patients undergoing primary percutaneous coronary intervention: Novel insights from an updte meta-Analysis. J American Heart association. 2016; 5 (7): e003515.
7. Martel N, Lee J, wells PS. Risk for heparin induced thrombocytopenia with un-fractionated and low molecular weight heparin thromboprophylaxis: a meta –analysis. Blood. 2005; 106 (8): 2710-15.
8. Andreou C., Maniotis C, K outouzis M. The rise and fall of anticoagulantion with Bivalirudin drug percutaneous coronary interventions: A review article. Cardiology and Therapy. 2017: 1-12.
9. Jolly SS, Yusuf S, Cairns J, Niemela K, Xaveir D., Widimsk YP et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomized parallel group, multicenter trial. The Lancet 2011; 377 (9775): 1409-20.
10. kastrati A, Newman FJ, Shulz S., Massberg S, Byrne R.A, Ference M et al. Abciximab and heparin versus bivalirudin for non-ST elevation myo- cardial infarction, New England Journal of Medicine. 2011; 365 (21): 1980-89.
11. Kastrati A, Newmann F.J, Mehilli J, Byrne RA, Buttner HJ et al. Bivalirudin versus unfractionated heparin during percutaneous coronary intervention New Eng J. med 2008; 359 (7): 688-96.
12. Shahzad A, Kemp 1, Mars C, Wilson K, Roome C, Cooper R et al. unfractionated heparin versus bivalirudin in primary pereutaneous coronary intervention (HEAT-PPCI): an open label, single centre, randomized controlled trial. The Lancet. 2014; 384 (9957): 1849-1858.
13. Karrowni W, Vyas A, Giacomino B, Schweizer M, Belvlins A, Girotras et al Radial versus femoral access for primary percutaneous interventions in ST-segment elevation myocardial infarction patients: a meta-analysis of randomized controlled trials. JACC: Cardiovascular Interventions. 2013; 6(8): 814-23.
14. Ruiz-Rodriguez E, Asfour A, Lolay G, Ziada KM, Abdel-latif AK. Systematic Review and Meta-analysis of Major Cardiovascular outcomes for radial versus Femoral access in patients with Acute coronary syndrome. NIH Public Access; 2016.
15. Lincoff AM, Bittle JA, Harrington RA, Feit F, Kleinman NS, Jackman JD et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trials. JAMA 2003, 289 (7):853-63.
16. Stone Gw, McLaurim BT, Cox DA, Beertrand ME, Moses JW et al. Bivalirudin for patients with acute coronary syndrome syndrome. New England J Medicine.2006; 355 (21): 2203-16.